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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/488,164	06/07/1995	JOHN J. KOPCHICK	7707-015	8450

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EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	32

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/488,164	KOPCHICK et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 17, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10-45, 62, 63, and 65-113* is/are pending in the application.

4a) Of the above, claim(s) *38, 39, 45, 63, 75-77, 79, 86-98, 100, 102-105, a* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-37, 40-44, 62, 65-74, 78, 80-85, 99, 101, and 106-109* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 31 is acknowledged. The traversal is on the ground(s) that Group I and II are combination/subcombination and restriction is improper. This is not found persuasive because the animal of Group II is not necessarily transformed with the DNA of claim 40(10). The animal of Group II could just as likely possess a natural transgene in which the expression has altered. This interpretation is based on the recitation of claim 10 which indicates that the DNA is "purified or non-naturally occurring", which encompasses naturally occurring molecules (non-statutory subject matter). Applicant further traverses the restriction by citing MPEP 809.02 and stating "the claims of group (III) which are dependent on allowable claims of group (I) must be rejoined. Applicant's arguments are not persuasive as no allowable claim has been indicated in the instant application. As was pointed out in paper #28, there is allowable subject matter, but Applicant has not presented a claim which is allowable. Therefore, there are no methods which are directed to an allowable product, and the methods will remain withdrawn.

Applicant traverses the "species restriction". Such a traversal is not persuasive as no "species restriction" was made in the instant application. Rather, a separate election of INVENTION was made for each DNA which is encompassed by the claims (see paper #28, page 3; reference to "patentably distinct DNA molecules"). Applicant further traverses by arguing that

all the claims were previously examined, and therefore, there is no burden of search or examination. This argument is not persuasive because an Examiner may make a restriction requirement at any point in prosecution. The instant application was originally filed with 8 claims. As prosecution has continued, more and more product claims have been added, in addition to method claims which may or may not be directed to the same product claims. As prosecution continues, the amount of information which requires searching increases, as well as the complexity of the claims which are being examined (the last addition of claims being in paper #29). Burden of search is established by separate classification and the necessity for non-coextensive literature searches for each DNA molecule encompassed by the claims.

The requirement is still deemed proper and is therefore made FINAL.

Response to Amendment

2. Claims 107-113 have been added in the amendment of paper #29, filed 21 June 2001. Claims 10-45, 62-63, 65-113 are pending in the instant application. Claims 38-39, 45, 63, 75-77, 79, 86-98, 100, 102-105 and 110-113 are withdrawn from consideration as being directed to a non-elected invention. (Applicant should note that claim 46 is not pending.) See 37 CFR 1.142(b) and MPEP § 821.03. Claims 10-37, 40-44, 62, 65-74, 78, 80-85, 99, 101, 106-109 are under examination in the instant application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

5. Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

6. Claims 10-37, 40-44, 62, 65-74, 78, 80-85, 99, 101, 106-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to subject matter of "a purified or non-naturally occurring DNA molecule" encoding a growth hormone receptor antagonist. However, in so far as the claims encompassed "a purified" DNA as compared to a "non-naturally occurring DNA molecule", the claims are directed to naturally occurring DNA molecules, which have not been described in the instant specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic and amino acid sequences and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, the claims fail to meet the written description provision of 35 USC 112, first paragraph in so far as the claims encompass naturally occurring DNA molecules. Applicant is

reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

It is noted that Applicant argues the allowability of claim 81 in paper #24. Applicant's statements and arguments are not persuasive, in light of the rejection for the recitation of "purified or non-naturally occurring". Suggested language to overcome the rejection as well as to simplify the claim language is as follows:

"A DNA molecule encoding a vertebrate growth hormone variant, said variant having an amino acid sequence comprising a substitution of any amino acid other than glycine or alanine at the glycine corresponding to Gly119 of bovine growth hormone, wherein said variant has growth hormone inhibitory activity".

Applicant is free to add the proviso discussed in the response.

Applicant's statements regarding claims 82-85 are not persuasive. The recitation of the structural limitations are not enabled by the instant specification, nor are such limitations supported by an adequate written description in the instant specification of the genus of molecules which are being claimed. The instant specification does not provide for a vertebrate growth hormone variant which retains an alpha helix which has some degree of % identity with human or bovine growth hormone, therefore, this is a new inventive concept. One cannot collect limitations piecemeal from the specification and present them together as a single concept where there is no

basis in the original specification for such a collection; this is deemed to be new matter and lacks written description.

The claims remain rejected for new matter as previously outlined in paper #23. Applicant argues this rejection in paper #24. Applicant argues that "reference vertebrate growth hormone" has "a common sense meaning" and was allowed in previous applications. These arguments are not persuasive. There is no basis for the concept of "reference vertebrate growth hormone" or for the new limitation of "first vertebrate growth hormone" and each application is examined on it's own merits. The above written claim provides for a reference point for making a mutation which results in a growth hormone which is an antagonist (i.e. has growth hormone inhibitory activity) without the issue of new matter and lack of written description which is raised with Applicant's language.

Applicant's arguments in paper #24, page 14, are confusing, at best. It would appear that Applicant is arguing that because the various growth hormone molecules have a degree of amino acid identity, that claims to molecules having a particular degree of amino acid identity are described. This argument is not persuasive because an adequate written description requires more than a mere statement that it is part of the invention. Such a recitation of varying degrees of % identity encompass mutation of growth hormone to the degree of variation of the claims, and the instant specification fails to provide a written description of the genus of molecules which vary from the naturally occurring growth hormones by the degree indicated in the claims.

Furthermore, a recitation of % identity between members of the growth hormone family is not a basis for claiming variant molecules which possess these various degrees of % identity (as well as a lack of enablement for the breadth of such claims), absent evidence to the contrary.

Applicant's "willing"ness to replace "90%" with other degrees of identity is noted, but would not remedy the rejection for the reasons of record. A disclosure of such a % identity is not a written description of a variant which possesses this degree of variation, nor is it enabling for the breadth of the claims.

Applicant's arguments of 10% binding affinity are noted, but not persuasive. It does not appear that the specification contemplates the inventive concept of a variant which has 10% binding affinity, and a statement that it is part of the invention is not a written description of those molecules which actually possess this characteristic, therefore, the instant specification lacks an adequate written description of this subject matter.

Applicant's arguments regarding claim 19 are noted, but the amendment to this claim does not remedy the rejection, as the claim still encompasses the breadth of substitution of all non-conservative amino acids.

Applicants arguments regarding claim 29 are noted but not persuasive. The instant specification does not contemplate a DNA molecule encoding a growth hormone receptor antagonist which comprises residues 96-133 of bovine growth hormone and is 50% identical to a reference vertebrate growth hormone, and therefore this inventive concept was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. The specification never pairs the 96-133 fragment with 50% identical, and this concept does not flow from the specification as originally filed, and therefore, lacks written description (in addition to lack of enablement).

Applicant asserts that basis for claim 34 is found at page 19, lines 30-34. This argument is not persuasive as the claim is directed to a vertebrate growth hormone, and the specification is directed to bovine growth hormone. The claim is a broader concept than the instant specification, and therefore, the claim is not supported by the instant specification as filed. Additionally, the specification does not support making a molecule which has the claimed function, therefore, the specification does not describe this inventive concept.

Applicant argues that basis for the exclusion of proline from claim 37 is "in the UpJohn Patent". However, there does not appear to be a basis in the instant specification for this negative limitation. It would appear that such a basis is essential material, which would need to be added to the specification if there is a basis for it's incorporation. The rejection will stand until this matter can be resolved.

Applicant argues support for claim 38 (in paper #24 at page 19). However, the specification still does not support the inventive concept of "which substitute amino acid has a greater alpha helical propensity than did the corresponding residue of said reference vertebrate hormone". There is no mention of substitution with a greater degree of propensity, but only that DNA which is degenerate should be prepared to encode amino acids with "acceptable alpha-

helical propensities". Therefore, this appears to be an new inventive concept which does not find basis in the specification as filed.

7. Claims 10-37, 40-44, 62, 65-74, 78, 80-85, 99, 101, 106-109 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record in paper #23.

Applicant argues this rejection beginning at page 19 of paper #24, continuing to page 24. Applicant indicates that complete structure is given for 8 variants, 6 of which are bovine growth hormone variants, 2 are human growth hormone variants, and only one of the 8 include multiple substitutions (3 in total). The key question is whether those species are representative of the claimed genus. As explained in the grounds of rejection, the subject matter which is claimed is directed to non-naturally occurring polypeptides which have at least 50% sequence identity to "a first vertebrate hormone", have a substitution which corresponds to amino acid position 119 of bovine growth hormone, and can be as short as 50 amino acids in length. First, the claims are not limited to those mutations which are exemplified in the instant specification, nor to those growth hormones exemplified in the instant specification. The specification only describes a handful of substitutions which provide the biological activity required by the claims and fails to teach or describe modifications which are commensurate in scope with the instant claims.. Therefore,

there is a lack of guidance or teaching regarding structure and function because there are only very limited examples provided in the specification and because there is no guidance found in the prior art which is commensurate in scope with the claims. Applicant asserts that because "conserved" and "non-conserved" positions are known for the various growth hormone proteins, there is a "known and disclosed correlation between activity and structure". This assertion is not persuasive. Just because amino acids are "conserved" or not does not permit the random substitution of these amino acids, nor does it provide for predictability in selecting amino acids to substitute at these positions. Receptor binding and biological activity are dependent on three-dimensional structure, and substitution of one amino acid in bovine for one amino acid in the human may have greater effects than predicted because those amino acids surrounding the substitution play important roles in structure, and therefore, function. The results of alanine scanning mutagenesis are such that they demonstrate the unpredictability of amino acid substitutions; substitution of "conservative" amino acids can have drastic effects on activity (i.e. increased receptor binding compared to loss of receptor binding compared to loss of the ability of the protein to be expressed). Therefore, there is no known or disclosed correlation between the structure which is recited in the claims (a particular degree of % identity) and the activity which is recited in the claims.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan

that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the instant claims except for the specific mutations which are provided in the examples of the specification which are limited to a very small portions of the growth hormone molecule. The specification does not provide a complete structure of those polypeptides which would be growth hormone receptor antagonist molecules as required by the claims. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus and the specification teaches a very limited number of embodiment. Therefore, the claims are directed subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. Claims 10-37, 40-44, 62, 65-74, 78, 80-85, 99, 101, 106-109 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA molecule encoding a vertebrate growth hormone variant, said variant having an amino acid sequence comprising a substitution of any amino acid other than glycine or alanine at the glycine corresponding to Gly119 of bovine growth hormone, wherein said variant has growth hormone

inhibitory activity, does not reasonably provide enablement for the breadth of the claims which are currently recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are broader than the enabling disclosure in that the instant specification teaches specific nucleic acid molecules which encode a vertebrate growth hormone variant which acts as an antagonist (8 specific examples). However, the instant claims are not enabled for their full breadth of 50% identity, etc. because it is not predictable which other modifications encompassed by the claims will encode a growth hormone molecule with the required activity. It would require undue experimentation to practice the current invention because one of ordinary skill in the art would not know which of those nucleic acid molecules that has the recited structural limitations would also encode a polypeptide with the required biological activity, the DNA is made, expressed in a host cell, and the protein is produced and tested. Therefore, the instant claims are a wish to know, and do not meet the requirements of enablement. Furthermore, the claims fail to recite sufficient structural elements to provide for the necessary function in that the structure of % identity is not sufficient for encoding a vertebrate growth hormone variant having the recited biological activity, therefore, the claims are not enabled. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. Appls, and Interf. 1986) and *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

The instant fact pattern is directly analogous in that what is claimed are nucleic acid molecules that have yet to be isolated or characterized for the activity recited in the application and thereby constitutes a "wish to know" rather than a reduction to practice, absent evidence to the contrary. The decisions of *In re Fisher*, Amgen Inc. v. Chugai, and *In re Wands* are relied upon in the instant rejection (see below) and by the court in a recent CAFC decision, Genentech, Inc. V. Novo Nordisk, 42 USPQ2d, 100 (CAFC 1997) because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and no on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiments is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims.

The issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990) and In re Wands, 8 USPQ2d, 1400 (CAFC 1988). The

factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims.

Due to the large quantity of experimentation necessary to generate the large number of molecules by the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of which of those molecules which meet the structural limitations of the claims would also meet the functional limitations of the claims. It is this additional characterization and inventive contribution that is required in order to obtain the functional and structural data needed to permit one to practice the claimed invention that constitutes undue experimentation.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 10-37, 40-44, 62, 65-74, 78, 80-85, 99, 101, 106-109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing with regard to "purified or non-naturally occurring". It is not clear if the claims are intending naturally occurring DNA, or if they are intending purified and unpurified DNA. Clarification may come after the written description rejection is addressed above.

The claims are indefinite with respect to the term "first vertebrate growth hormone". This term is nowhere defined in the specification and does not have a well-known art-recognized meaning. Therefore, one cannot determine the metes and bounds of the claimed polypeptide.

The claims are indefinite for the recitation of "differs therefrom solely in that", which is followed by additional modifications (see claim 10 for example). If the DNA is to encode a protein that differs "solely", then it is not clear how it can have other variations in addition. What is really encompassed by the recitation of the variations structural limitations is confusing as it is not clear which are present or excluded by the claims.

The recitation of "coding sequence encoding" is redundant in claim 107. The recitation of "an amino acid substitution of an amino acid" is redundant. The recitation of "at the position corresponding to position 119 of bovine growth hormone" is not definite, in that depending on the nature of the bovine molecule (i.e. bacterially produced or naturally occurring), the numbering

of the molecule may change (i.e. the presence of an N-terminal methionine, for example). The claim should recite that it is the glycine at position 119 which is the corresponding amino acid. Please review the claim provided in the office action above which would be allowable.

Claim 108 is indefinite for the recitation of "said position". There are several positions enumerated in claim 107, therefore, it is not clear which "said position" is intended.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December 31, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud